NeuroImage 52 (2010) 956–972

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Understanding the relationships between spike rate and delta/gamma frequency bands of LFPs and EEGs using a local cortical network model

Alberto Mazzoni [a,b], Kevin Whittingstall [c], Nicolas Brunel [b,d,e], Nikos K Logothetis [c,f], Stefano Panzeri [a,*]

[a] Department of Robotics, Brain and Cognitive Sciences, Italian Institute of Technology, via Morego 30, 16163 Genoa, Italy
[b] Institute for Scientific Interchange, viale Settimio Severo 65, 10133, Turin, Italy
[c] Max Planck Institute for Biological Cybernetics, Spemannstrasse 38, 72076, Tuebingen, Germany
[d] Laboratory of Neurophysics and Physiology, Université Paris Descartes, Rue des Saints Pères 45, Paris, France
[e] CNRS UMR 8119, Paris, France
[f] Division of Imaging Science and Biomedical Engineering, University of Manchester, The Mill, PO Box 88, Manchester M60 1QD, UK

ARTICLE INFO

Article history:
Received 10 September 2009
Revised 4 December 2009
Accepted 8 December 2009
Available online 21 December 2009

Keywords:
Electroencephalography
Delta rhythm
Gamma rhythm
Integrate-and-fire network
Field potential
Natural stimuli
Oscillations
Cross-frequency coupling

ABSTRACT

Despite the widespread use of EEGs to measure the large-scale dynamics of the human brain, little is known on how the dynamics of EEGs relates to that of the underlying spike rates of cortical neurons. However, progress was made by recent neurophysiological experiments reporting that EEG delta-band phase and gamma-band amplitude reliably predict some complementary aspects of the time course of spikes of visual cortical neurons. To elucidate the mechanisms behind these findings, here we hypothesize that the EEG delta phase reflects shifts of local cortical excitability arising from slow fluctuations in the network input due to entrainment to sensory stimuli or to fluctuations in ongoing activity, and that the resulting local excitability fluctuations modulate both the spike rate and the engagement of excitatory–inhibitory loops producing gamma-band oscillations. We quantitatively tested these hypotheses by simulating a recurrent network of excitatory and inhibitory neurons stimulated with dynamic inputs presenting temporal regularities similar to that of thalamic responses during naturalistic visual stimulation and during spontaneous activity. The network model reproduced in detail the experimental relationships between spike rate and EEGs, and suggested that the complementariness of the prediction of spike rates obtained from EEG delta phase or gamma amplitude arises from nonlinearities in the engagement of excitatory–inhibitory loops and from temporal modulations in the amplitude of the network input, which respectively limit the predictability of spike rates from gamma amplitude or delta phase alone. The model suggested also ways to improve and extend current algorithms for online prediction of spike rates from EEGs.

Introduction

Electroencephalography (EEG) is one the most important tools for non-invasively studying brain activity in humans at fine time resolution (Lopes da Silva and Van Rotterdam, 1987; Nunez, 1981). Despite its wide use in clinical applications and in neurophysiological research, the exact relationships between the surface EEG and the underlying physiological events at the cellular and network level remain only partly known. Early studies (Creutzfeldt et al., 1966a, b; Klee et al., 1965) demonstrated that a prominent contribution to cortical surface EEGs comes from excitatory and inhibitory synaptic potentials (mostly from pyramidal neurons but perhaps also from spiny and aspiny stellate cells, see (Murakami and Okada, 2006)), and from afterdischarges not directly related to cellular activity (Creutzfeldt et al., 1966a, b; Klee et al., 1965). Other studies (Granit et al., 1963; Juergens et al., 1999; Kamondi et al., 1998; Mitzdorf, 1987) showed that these mechanisms also contribute to the generation of the Local Field Potential (LFP), an intracortical signal which shares similarities with the EEG but is more localized (Katzner et al., 2009). However, we still do not know which aspects of the time course and frequency content of the surface EEG allow an estimation of the time course of the spiking activity of cortical projection neurons, i.e. the output of the cortical site. This is clearly an important question to address for several reasons. First, progress in estimating the strength and timing of cortical spike rates from EEGs would greatly increase our understanding of the neural computations underlying the recorded EEG signal. Second, understanding how macroscopic and mesoscopic signals such as EEGs and LFPs relate to the output of a very local neuronal computation (whose results is carried by the spikes of pyramidal neurons) is a fundamental empirical step in constructing models linking large scale dynamics of cortex to computations of local networks.

Recently, we made progress in this direction (Whittingstall and Logothetis, 2009) by showing that, in macaque primary visual cortex, the time course of the spike rate can be predicted by a combination

* Corresponding author.
E-mail address: stefano.panzeri@iit.it (S. Panzeri).

1053-8119/$ – see front matter © 2009 Elsevier Inc. All rights reserved.
doi:10.1016/j.neuroimage.2009.12.040

of the instantaneous delta-band (2–4 Hz) phase and gamma-band (30–100 Hz) amplitude of the concurrently recorded surface EEG. This was observed both during visual stimulation with naturalistic movies and during stimulus-free periods. Consistent findings were also obtained when predicting spike rates from intracortical LFPs rather than from EEGs (Rasch et al., 2008; Whittingstall and Logothetis, 2009). Interestingly, the cross-frequency coupling (i.e. the coupling of the phase of a slower frequency with the amplitude of a faster rhythm) which has been shown to determine the strength and timing of spiking activity in visual cortex (Whittingstall and Logothetis, 2009) has also been consistently observed in neocortex (Canolty et al., 2006; Lakatos et al., 2005) and hippocampus (Bragin et al., 1995; Lisman, 2005) and is thought to be central for a number of cognitive and sensory processes (Jensen and Colgin, 2007; Lisman, 2005; Lisman and Idiart, 1995; Schroeder and Lakatos, 2009).

These findings raise the important question of what are the mechanisms which generate cross frequency-coupling, and how cross-frequency coupling correlates to the timing and strength of spiking activity. Answering these questions would not only allow better insights into the mechanism regulating cortical dynamics, but has obvious implications for improving the prediction of spiking activity from EEGs and LFPs.

Here we aim at explaining these empirical findings by hypothesizing that the EEG-LFP delta phase reflects shifts of the cortical excitability arising from low-frequency (delta range) fluctuations in the strength of the input to the local network, and that these changes in excitability modulate both the output spike rate and the engagement of excitatory–inhibitory loops producing gamma-band oscillations, which in turn leads to the observed three-way relationships between spike rate, gamma amplitude and delta phase. Slow (delta range) input fluctuations may be either mediated by thalamo-cortical connections and arise from slow variations in thalamic firing reflecting responses to the relatively slow and regular changes present in naturalistic stimuli, or may be mediated by cortico-cortical connections and originate from slow and spatially extended fluctuations of ongoing cortical activity.

To test quantitatively this hypothesis, we simulated a recurrent network of integrate-and-fire neurons with excitatory–inhibitory connections stimulated with dynamic inputs with temporal regularities similar to that of thalamic responses during naturalistic visual stimulation and during spontaneous activity; we then carefully studied the dependence between the simulated EEG-LFP frequency bands and the spike rate of the simulated pyramidal neurons and how this dependence is modulated by different biophysical mechanisms; and we compared in detail the spike-EEG/LFP relationships found in the model and in real EEG/LFP recordings of awake and anaesthetized macaques during stimulation with naturalistic movies or in absence of visual stimuli.

Methods

All experiments conducted on macaques were approved by the local authorities (Regierungspräsidium Tübingen) and are in full compliance with the guidelines of the European Community (EUVD 86/609/EEC) for the care and use of laboratory animal.

Recordings of EEGs, LFPs and spike from the primary visual cortex of awake macaques

Methods were fully reported elsewhere (Whittingstall and Logothetis, 2009), to which we refer for more details. In brief, EEG recordings were made from two non-anesthetized monkeys (*Macaca mulatta*) using a Ag/AgCl ring electrode (impedance below 20 kΩ) positioned over the visual cortex. EEG signals were amplified and filtered into a band of 0.2–250 Hz (Brain Products, Munich, Germany) and digitized at 5 kHz. The EEG ring electrode of interest was placed at the base of a recording chamber positioned over primary visual cortex (V1), made from PEEK (polyetheretherketone; TecaPEEK, Nufringen, Germany) and secured to the skull. The EEG ring electrode rested on the skull and small circular openings (under the center of the EEG ring electrode) in the skull were made to access cortical neurons. In one monkey, a 5 mm circular patch was resected, while in the other monkey, a 2 mm circular patch was resected in order to access the underlying cortex. Tungsten microelectrodes (FHC Inc., Bowdoinham, Maine, 0.5 to 2 MΩ) were lowered through the middle of the EEG ring electrode into the cortex in order to obtain spiking activity and LFPs. The extracellular signals obtained from these intracortical tungsten microelectrodes (whose tips were typically, but not always, positioned in the upper or middle cortical layers) were high-pass filtered (1 Hz, digital two pole Butterworth filter), amplified (Alpha Omega Engineering) and digitized at 20.83 kHz. A frontal EEG electrode placed on the scalp was used as reference.

The LFPs were extracted by band-pass filtering the neural signal in the 2- to 125-Hz range and resampling at a rate of 250 Hz. Filtering was done using Kaiser filters with sharp transition bandwidth (1 Hz), small passband ripple (0.01 db) and high stopband attenuation (60 dB). A mirroring technique was used to reduce edge artifacts during filtering and forwards and backwards filtering was used to eliminate phase shifts. The very same filtering technique was applied to further bandpass all the real neural data and the simulated to create the signal bandpassed in the various frequency bands (such as delta and gamma band). The instantaneous amplitude and phase of the bandpassed signals were obtained by taking respectively the modulus and angle of the complex time series obtained through the Hilbert transform of the bandpassed signal. Circular statistics analysis on the so obtained phase distributions was performed with the CircStat MATLAB (The Mathworks, Natick, MA) Toolbox described in Berens (2009).

To extract spike times, following Quiroga et al. (2004), we band-pass filtered (with the same filtering techniques described above) the extracellular signal from intracortical electrode at 300–4000 Hz, and we used for spike detection an amplitude threshold of 4 standard deviations (sds) of the mean amplitude. A spike was recognized as such only if the last spike occurred more than 1.5 ms earlier. This threshold approach for spike detection is appropriate for spike times but not for the isolation of single units. Thus, the spikes used for the analysis represented the spiking activity of a small population of cells rather than well-separated spikes from single neurons (Quiroga et al., 2004).

Visual stimuli consisted of naturalistic commercially available movies (30 Hz frame rate), from which 5-s clips were presented on a computer screen (field of view: 90 Hz refresh); each stimulus was repeated 30–40 times per experimental session. Data were acquired while the animals performed a visual fixation task (9 s fixation period, 2.0–2.8 deg fixation window). Each 9-s-long trial consisted of 2 s of fixation of a small (0.2 deg) fixation spot on dark background, followed by 5 s of movie presentation during fixation of the same spot, finally followed by 2 of continued fixation of the spot on dark background. When analyzing movie-driven activity, we discarded from further analysis the first second of data as it mainly consisted of a transient response to the stimulus onset. We also analyzed data recorded from the awake monkey during the first period of fixation of spot on dark background prior to the movie, and we will refer for brevity to these data as collected during “spontaneous activity” to mean that they are collected in absence of the movie stimulus.

Recordings in primary visual cortex and in the lateral geniculate nucleus of anaesthetized monkeys

We also analyzed recordings from 76 sites in V1 and from 8 sites in the dorsal lateral geniculate nucleus (LGN) that were obtained in a separate set of experiments involving four adult rhesus monkeys (*Macaca mulatta*). Full details of experimental procedures were given elsewhere (Belitski et al., 2008; Rasch et al., 2008). In brief, recordings were obtained while the animals were anaesthetized (remifentanyl,